REMARKS

The fee for a three month extension of time should be charged to Deposit Account No. 02-1818. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 02-1818. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 02-1818.

A Change of Correspondence Address accompanies this paper. A Supplemental Information Disclosure Statement is being filed on the same day herewith, under separate cover.

Claims 1-6, 9, 12-16, 18 and 21-23 are pending. Claims 7, 8, 10, 11, 20 are cancelled without prejudice or disclaimer. Claims 3-5, 13 and 15, which are directed to non-elected species, are withdrawn. They are retained pending allowance of a generic claim. Applicant reserves the right to file continuing/divisional applications to non-elected, cancelled and unclaimed subject matter.

Claims 1-6, 9, 12-15 and 18 are amended. Claim 1 is amended to recite that the administered microorganism is a bacterium, and also to include the limitations of cancelled claim 20. Claim 1 also is amended for clarity to recite that the bacterium is monitored in the subject to detect accumulation bacterium at or in a wounded or inflamed tissue "within the subject," and also to eliminate redundant language (*i.e.*, wound and wounded tissue) as suggested by the Examiner. Claims 1-6, 18 are amended to replace "microorganism or cell" with "bacterium." Claim 9 is amended to depend from pending claim 1, which includes the limitation of cancelled claim 7. The remaining amended claims are amended for clarity and proper dependence. Claim 23, which is added, recites that the bacterium of claim 1 is administered intravenously, intraperitoneally, subcutaneously, intramuscularly, topically or intradermally. Basis can be found in the application as filed, for example on page 13, lines 1-2. Therefore, no new matter is added.

I. OBJECTION TO CLAIM 1 – INFORMALITY

On page 3 of the Office Action, the examiner asserts that "there appears to be no difference between a wound and wounded tissue as used in the application. Therefore, the recitation of wound or wounded tissue is redundant." Applicant submits that a wound is intended to encompass any lesion or injury to any tissue in a subject. Accordingly, a wound is encompassed by the term "wounded tissue" as used in the application. Claim 1 is amended

herein to recite a "wounded or inflamed tissue" in place of "a wound, wounded tissue or inflamed tissue," thereby obviating this objection.

II. REJECTION OF CLAIMS 33-47 AND 51-80 UNDER 35 U.S.C. §112, FIRST PARAGRAPH – SCOPE OF ENABLEMENT

Claims 1, 2, 6, 7, 9, 12, 14, 16, 18 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, as being broader than the enabling disclosure.

On page 3, the Examiner asserts that:

> the specification, while being enabling for a method for detecting a wound comprising administering a bacterial cell selected from *E. coli* and attenuated *S. typhimurium*, or attenuated *V. cholerae* does not reasonably provide enablement for a method of detecting a wound or inflammation in a subject comprising administering any microorganism or cell to a subject and detecting the accumulation of the microorganism or cell at a wound or inflamed tissue in the subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection respectfully is traversed. First, it is noted that the claim 9, which is directed to methods that employ an attenuated *Salmonella typhimurium*, an attenuated *Vibrio cholerae*, an attenuated *Listeria monocytogenes* and *E. coli*, which the Examiner states are enabled. Thus, claim 9 is outside the purview of this rejection.

Relevant law

To satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." *In re Marzocchi et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz*, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular

embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the subject matter *as claimed*. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Arguments

In setting forth the enablement rejection, the Examiner has alleged that the scope of the claims are not enabled in view of the factors enumerated in *In re Wands*. The Examiner has relied only on alleged unpredictability in the art with respect detection of wounded and inflamed tissues using any microorganism or cell. Predictability is only one of the nine or ten factors that must be considered and weighed. Further, the Examiner has provided no sound scientific basis for such conclusion. As evidenced below, the state of the art, knowledge of those of skill in the art, the teachings in the application, and the working examples, as well as the demonstrated predictability and reproducibility of the methods, evidence that it would not require undue experimentation to practice the methods as claimed.

Consideration of the all factors enumerated in *In re Wands*, including the scope of the claims, the teachings and examples in the specification for administering and detecting bacteria for detection and treatment of wounded and inflamed tissue, the high level of skill of those in this art, the advanced knowledge of those of skill in the art, the fact that it is predictable given the teachings of the instant application and the state of the art at the time of the effective date of the claims, it would not require undue experimentation for one of skill in

the art to practice the methods as claimed herein to introduce a detectable bacterium into a subject for the detection of a wounded or inflamed tissue within a subject. Furthermore, it does not require undue experimentation to select a bacterium with the properties as described in the application to practice the claimed methods. Specifically, one of skill in the art can select a bacterium that is detectable, non-pathogenic or attenuated, replication competent and that is recognized by the immune system of the subject to whom the bacterium is administered. As discussed, below in more detail, the specification, demonstrates that a bacterium with such properties predictably localizes to wounded and inflamed tissues, and can be detected. Further, since the bacterium accumulates in wounded and inflamed tissues it delivers encoded proteins thereto, including proteins expressed for therapy of wounded and inflamed tissues.

As established below, the instant claims are directed to methods that employ bacteria that are detectable and that can be administered to subjects. As shown in the application that bacteria that are non-pathogenic and recognized by the immune system accumulate in any wounded or inflamed tissues. The bacteria include those that are inherently detectable, such as heavy metal accumulating bacteria, or are modified to include a detectable product or to encode products and substrates to produce or induce a detectable signal. Such detectable products and signals are well known. Methods for detecting such bacteria in subjects are known and also are described in the application.

Bacteria that can be administered and that are non-pathogenic and recognized by the immune system are known, and exemplified and described in the application. Such bacteria, not only are known and exemplified, they also can be prepared, as taught in the application, for detection of wounded and inflamed tissues. The instant application provides a new use and method using known materials and detection/visualization methods. The use of bacteria and their accumulation in tumor tissues is known in the art. The instant application shows that such bacteria also accumulate in wounded and inflamed tissue within a subject and that known detection/visualization methods can be employed to detect accumulation of the bacteria and thereby detect wounded and inflamed tissues.

As recited in the claims, the bacteria are not *any* bacteria, but are bacteria that are (a) detectable; (b) able to replicate in the subject to whom the bacteria are administered; (c) non-pathogenic or attenuated; and (c) recognized by the immune system of the subject. The specification teaches numerous species of bacteria suitable for practice of the method and how to identify other species, the specification includes several working examples, with a

variety of bacterial species, and teaches of the properties of bacteria for use in the methods. Those of skill in the art, who have a high level of skill, know of such bacteria and how to employ them for administration and visualization. Visualization/detection methods are known to those of skill in the art and also are described in the specification. Further, the specification demonstrates that the method is reproducible (*i.e.*, predictable). Thus, based on these factors, the factors enumerated in *In re Wands*, which include the scope of the claims, the teachings and examples in the specification, level of skill in the art, knowledge of those of skill in the art and state of the prior art, and predictability, it would not require undue experimentation for one of skill in the art to practice the methods as claimed to introduce detectable bacteria into a subject for the detection of a wound, wounded tissue, inflammation or inflamed tissue.

1. Breadth of the claims

Claim 1 recites:

> A method, comprising:
> administering to a subject in whom the presence or absence of a wounded tissue or inflamed tissue or a disease associated therewith is to be detected, a bacterium, wherein:
> the bacterium is detectable in the subject;
> the bacterium replicates in the subject;
> the bacterium is not pathogenic to the subject and is recognized by the immune system of the subject; and
> the bacterium is not targeted; and
> monitoring the subject to detect the accumulation of the bacterium at or in a wounded tissue or inflamed tissue within the subject, whereby, detection of the accumulation indicates the location of the wounded tissue or inflamed tissue within the subject.

Claim 2 is dependent on claim 1 and recites that the bacterium encodes a protein(s) for the therapy of the detected wounded or inflamed tissue. Other dependent claims specify therapeutic proteins, detectable proteins or proteins that induce a detectable signal and detection methods.

As noted, Applicant reserves the right to prosecute cancelled subject matter, such as that to viruses, in continuing/divisional applications. As pending, the claims are tailored to the teachings and working examples in the specification. As discussed below, bacteria that meet the recited criteria (replicates in the subject, are not pathogenic to the subject, and are recognized by the immune system of the subject) are well known and numerous examples are taught and exemplified in the specification. Further detectable bacteria or bacteria modified

for detection also are taught and exemplified in the specification and also are well known to those of skill in the art. Thus, the claims are of the same scope as the specification

2. Level of Skill in the Art

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, further evidences the high level of skill in this art.

3. State of the Prior Art

At the time of filing of the application, a broad body of knowledge had amassed in the areas of microbiology, molecular biology, genetics, and medicine including many technical procedures covering the generation, preparation, administration and detection of bacteria, viruses, and cells, including production of recombinant organisms using recombinant nucleic acid techniques, and expression and detection of exemplary detectable proteins, which are employed in the claimed methods. Numerous such procedures are referenced in the specification and/or described in the application and/or described in prior art submitted by Applicant to the Patent Office in connection with the instant Application.

The art provides numerous species of microorganisms that can be used in the methods provided in the instant application. The art provides bacteria that can be administered, including attenuated or non-pathogenic bacteria. For example, Pawelek *et al.* (WO 96/40238) provides numerous examples of attenuated or non-pathogenic bacteria and other microorganisms that can be administered to mammalian subjects (see Table 1 of WO 96/40238). The reference provides techniques for attenuation of the bacteria and methods for engineering the bacteria to express heterologous genes. Also provided are methods for selection of suitable bacteria for administration.

Numerous detectable proteins were known in art at the time of filing that can be used in the claimed methods. Exemplary detectable proteins include luminescent or fluorescent proteins, such as luciferase from *Vibrio harveyi* (Belas *et al.*, *Science* 218 (1982), 791-793) and from *Vibrio fischerii* (Foran *et al.*, *Nucleic Acids Res.* 16 (1988), 177), firefly luciferase (de Wet *et al.*, *Mol. Cell. Biol.* 7 (1987), 725-737), aequorin from *Aequorea victoria* (Prasher *et al.*, *Biochem.* 26 (1987), 1326-1332), Renilla luciferase from *Renilla reniformis* (Lorenz *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 88 (1991), 4438-4442) and green fluorescent protein from *Aequorea victoria* (Prasher *et al.*, *Gene* 111 (1987), 229-233). Furthermore, expression of proteins that can be employed for detection via magnetic resonance or positron emission

imaging were known (see, *e.g.*, WO 01/25399, Weissleder *et al.* (2000) *Nature Medicine* 6(3): 351-354, Weissleder *et al.* (1992) *Magnetic Resonance Quarterly* 8(1): 53-63, Tjuvajev *et al.* (2001) *Journal of Controlled Release* 74(103): 313-315, Moore *et al.* (1998) *Biochimica et Biophysica Acta* 1402(3): 239-249).

Techniques for construction light-emitting bacteria were known at the time for filing of the instant application. For example, bacteria engineered to carry the *lux-cdabe* operon for expression of bacterial luciferase and administration methods for infecting mice with such bacteria were well-known. Meighen *et al.*, *J. Bacteriol.* 174 (1992), 5371-5381 and Lee *et al.*, *Eur. J. Biochem.* 201 (1991) 161-167, Fernandez-Pinas *et al.*, *Gene* 150 (1994), 169-174, describe the lux operon and construction of a wide variety of bacteria that contain the operon for expression of the bacterial luciferase.

Expression of detectable proteins by microorganisms for detection of microorganisms within other organisms are described in the art and include, for example, expression of luxAB in *Rhizobia* residing within the cytoplasm of cells of infected root nodules (Legocki *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 83 (1986), 9080-9084; O'Kane *et al.*, *J. Plant Mol. Biol.* 10 (1988), 387-399), *Bacillus subtilis* and B*acillus megatherium* expression of lux A and lux B fusion genes (Fab2) in insect larvae and worms (Escher *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 86 (1989), 6528-6532), and *Pseudomonas* or *Ervinia spp.* expression of pathogen-activated PAL promoter-bacterial luciferase fusion gene in transgenic Arabidopsis plants, tomato plants and stacks of potatoes (Giacomin *et al.*, *Plant Sci.* 116 (1996), 59-72). Expression of light-emitting bacteria in mammalian subjects is described in Contag *et al.*, *Mol. Microbiol.* 18 (1995), 593-603.

Methods for detection of microorganisms, such as bacteria, that express light-emitting molecules also were known at the time of the earliest priority date. International PCT application No WO01/14579, which describes the use of targeting bacteria to tumor antigens for detection of tumors, describes many non-pathogenic bacteria that replicate in subjects, as well as methods for detection thereof. Numerous other references describe bacteria and methods for detection. For example, luminescent and fluorescent signals produced by such proteins can be detected with low light imaging cameras or fluorescent imaging devices (see, Engebrecht *et al.*, *Science* 227 (1985), 1345-1347; Legocki *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 83 (1986), 9080-9084; Chalfie *et al.*, *Science* 263 (1994), 802-805).

Contag *et al.* (U.S. Patent No. 6,217,847) describes methods of *in vivo* imaging, including bacteria and viruses that express detectable proteins. Contag *et al.*, which requires

targeting of bacteria, not accumulation, provides numerous examples of light-emitting proteins that can be expressed by the bacteria (see, *e.g.* columns 9-10) and methods for detecting the bacteria including several types of photodetection and amplification devices (see, *e.g.* columns 16-17). In addition, the reference also provides a detailed description of the methods that can be employed to image the bacteria *in vivo* (see, *e.g.* columns 17-20).

Zhao et al. (2001) *Proc. Natl. Acad. Sci. U.S.A.* 98(17) 9814-9818 describes methods of engineering GFP-expressing *E. coli* for *in vivo* detection. Methods for preparing, administering and detecting the bacteria *in vivo* are provided. The reference describes a method of tracking the fluorescent signal emitted by the bacterium in a live animal over time. The reference thus describes methods of spatial and temporal imaging of bacterial localization within a subject.

In addition, techniques and methods for expression and *in vivo* detection of fluorescent and bioluminescent molecules are known (see, *e.g.*, Belas *et al.*, *Science*, 218: 791-793 (1982), Chalfie et al, *Science* 263: 802-805 (1994), Contag *et al.*, *Mol. Microbiol.* 18: 593-603 (1995), Greer III, *et al.*, *Luminescence*. 17(1):43-74 (2002), Rodriguez *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* U.S.A., 85: 1667-1671 (1988), Rocchetta *et al.*, *Antimicrobial Agents and Chemotherapy* 45(1): 129-137 (2001), Yang *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 97(22): 12278-12282 (2000), Wang Y. *et al.*, *Mol Genet Genomics*. 268(2):160-8 (2002), Lamberton *et al.*, *Proceedings of the 12th International Symposium on Bioluminescence & Chemiluminescence:* 5-9 April 2002, Robinson College, University of Cambridge, UK, p 3.22 (2002)).

Techniques and methods for use of other detectable molecules for *in vivo* labeling such as radionucleotides for MRI or PET imaging are known (see, *e.g.*, Welling *et al.*, Eur J Nucl Med. 27(3):292-301 (2000), Adonai *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* 99: 3030-3035 (2002), Welling *et al.*, *Nucl Med Biol.* 29(4):413-22 (2002), Nibbering *et al.*, Nucl Med Commun. 19(12):1117-21 (1998), Weissleder, T. *et al.*, *Nat. Med.* , 6(3): 351-354 (2000) and Berger, F. and S.S. Gambhir, *Breast Cancer Research* 3: 28-35 (2001); other references describing imaging methods, include, *e.g.*, references cited in Massoud *et al. Genes & Development* 17: 545-580 (2003)). Engineering bacteria to accumulate metals and metal-binding proteins were well-known before the earliest priority date of the instant application.

The references cited above are not an exhaustive list of the references that were available to one of skill in the art at the time filing. They are a representative selection of art to demonstrate the existence large volume of information regarding tested and reliable

procedures available at the time of filing of the instant application and thus evidence the advanced state of the art at the relevant time with regard to known methods of methods of selection of, modifying, administering and detecting microorganisms and cells, including bacteria and viruses. They evidence the advanced state of the art with respect to identification of bacteria with properties recited in the claims, and methods for detection/visualization.

4. Nature of the Claimed Subject Matter

The claimed subject matter is a method for detecting wounded and inflamed tissues/sites by administration of bacteria that are detectable, non-pathogenic, replication competent and recognized by the immune system. The application teaches and demonstrates and exemplifies that such bacteria accumulate in wounded/inflamed tissues/sites. As discussed above, the claims are directed to methods of use of known materials (bacteria) that can be detected/visualized by known methods. Hence, the reagents used in the methods and the detection methods should not be at issue. Once Applicant describes the use of such reagents for detection of wounds/inflamed tissues/sites and describes bacteria and properties thereof more should not be needed for one of skill in the art to practice the methods as claimed.

5. Predictability of the method

The specification provides three working examples with three different species of bacteria, and shows that all, as described in the specification accumulate wounded and inflamed tissues/sites. The data show that an animal with a wounded or inflamed tissue can be administered an attenuated, non-pathogenic bacterium that is recognized by the immune system and the administered bacteria accumulates in the wounds or inflamed tissues, thereby allowing detection of the wound.

Practice of the method with other bacteria in addition to the exemplified species and detection methods is routine, since the claims and specification recite the properties of the bacteria required, including that they are non-pathogenic and recognized by the immune system, and the specification describes such bacteria. As described above, a variety of non-pathogenic or attenuated bacteria recognized by the immune system were known at the time the priority date of the application, as were methods for detection thereof for visualization of tissues/sites as described above (see references discussed above, and the specification as discussed herein). Hence there is no basis to conclude that successful practice of the method is not predictable.

6. Amount of Direction and Guidance Provided by the Specification

The specification describes the generation, administration, and detection of microorganisms and cells, including bacteria, for the detection of a wound, wounded tissue, an inflammation site, inflamed tissue, or a disease or condition associated thereof. The teachings of the specification describe how to select bacteria or use in the methods, how to administer them, how to detect them *in vivo*, and provides instruction for modification of bacteria to express proteins, including therapeutic proteins and detectable proteins. The specification teaches the features of the bacteria for use in the methods (*i.e.*, that they are, non-pathogenic or attenuated and recognized by the immune system). It is taught that such detection is useful for visualization of and diagnosis of the wounded or inflamed tissues and for therapy of the wounded or inflamed tissues, including identification of site for subsequent application of a therapeutic agent (page 5, line 25 through page 6, line 6) or directed expression of proteins suitable for therapy at the affected site.

The specification teaches examples of proteins that can be expressed by the microorganism or cell for diagnosis and treatment (page 6, line 8). For example, diagnostic proteins, such as fluorescent, bioluminescent, and metal binding proteins (see, *e.g.*, pages 7, line 13-18, pages 8-10) and therapeutic proteins, such as various growth factors and enzymes (see, *e.g.*, pages 6-7) can be expressed by the microorganisms or cells and are described. Exemplary vectors including viral, mammalian and bacterial vectors for the expression of such proteins are also exemplified (see, *e.g.*, page 8).

The specification teaches exemplary bacteria, such as attenuated *Salmonella typhimurium*, attenuated *Vibrio cholera*, attenuated *Listeria monocytogenes* and *E. coli.*

The specification further teaches methods of administering the bacteria, including routes of administration and factors to be considered for assessing methods of administration and dosages (see, *e.g.* Examples). The specification also provides examples of diseases and conditions that are associated with wounded or inflamed tissue. The specification also provides details for administration of therapeutic proteins and molecules (see, *e.g.*, pages 14-15) with the bacteria.

7. Working Examples

The specification provides working examples and descriptions of the generation, administration, and detection of microorganisms and cells for the detection of a wound, wounded tissue, an inflammation site or inflamed tissue. The working examples of bacterial accumulation at wounded or inflamed sites provide sufficient teachings, in combination with

what was known to those of skill in the art at the time of the instant application's earliest priority date, to generate, administer, and detect a microorganism or cell regardless of the microorganism or cell that is used provided that the microorganism or cell is detectable. For example, techniques for use in the administration and detection of luminescent bacteria in an animal model for wounded tissues are provided in Examples 1, 2 and 3, including examples of plasmid constructs that can be used for bacterial expression of bacterial luciferase, administration methods (*e.g.* intravenous injection), methods and equipment employed for detection, and methods for generating wounded tissue for the experiment, including incision wounds, ear tags wounds, and surgical heart defects. Such techniques are applicable to use of the methods in subjects with existing wounds or inflamed tissues. Furthermore, the examples provide guidance for one of skill in the art, if needed, to use animal models for testing particular detectable microorganisms and cells. For example, methods and instruction are provided for analysis of accumulation in wounded/inflamed tissue versus unaffected tissue in an animal model, including whole body luminescence detection as well as organ excision and cell culture methods for analyzing various tissues of the animal model.

The working examples exemplify the teaching using three diverse species of bacteria (*S. typhimurium*, *V. cholera*, and *E. coli*). Each of these bacteria were modified to express a protein that induces a detectable signal, a bacterial luciferase, which is expressed from the *lux-cdabe* operon. Also expressed from the *lux-cdabe* operon are proteins involved in the production of the substrate for the luciferase, which allows detection of the bacteria. The examples demonstrate exemplary methods of systemic administration of the microorganisms by intravenous administration. Following intravenous administration, the bacteria are initially carried throughout the body via the blood stream as shown in Figure 1. After a period of time, both *S. typhimurium* and *V. cholera* were shown to accumulate in cutaneous wounds and inflamed tissues of the ear (Example 2). In Example 3, *E. coli* was shown accumulate in wounded heart tissue. In all cases, the bacteria was efficiently cleared from non-wounded tissues by either the subject's immune system or organs normally involved in bacterial clearance, such as the liver and spleen. Given the normal function of the liver and spleen in bacterial clearance, initial accumulation of bacteria in the liver and spleen was observed in some instances.

The specification teaches that these are exemplary and that the examples can be extrapolated and use for any species. Further, Applicant is not required to provide data or

illustrative examples in support of every embodiment within the scope of a claim. *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973)).

8. Quantity of Experimentation

The type and quantity of experimentation in light of the teachings of the specification and knowledge and skill of those in the art is routine. As discussed above, the specification teaches the properties of bacteria for use in the methods and exemplifies the methods with three different species. Those of skill in the art are familiar with other suitable species, as well as detection/visualization methods. Accordingly, any experimentation with different species would be routine to confirm, if necessary, that a particular species is accumulates in wounded/inflamed tissues, and optimization of parameters for such species. The specification teaches and exemplifies how to test species and parameters to optimize.

As evidenced by the state of the art discussed above, any needed manipulations to prepare bacteria have been practiced for many years. Furthermore, detection techniques for *in vivo* detection and methods to optimize such techniques are also well known. The application also provides ample guidance for routine testing of a microorganism or cell for use in diagnosis or treatment of wounded or inflamed tissues. "A considerable amount of experimentation is permissible, if it is merely routine..." *In re Wands* 858 F.3d 731, 737.

Conclusion

It respectfully is submitted, that although use of bacteria that are recognized by the immune system and replicate in the subject for detection of wounded or inflamed tissues was not known as of the earliest claimed priority date of the subject application (as this is the presently claimed subject matter), the specification provides working example demonstrating three different species of bacteria and showing that each accumulates in wounded/inflamed tissue, and the specification teaches the requisite properties of bacteria for use in the methods. Further, species of bacteria that at are recognized by the immune system and that are nonpathogenic or attenuated that can be used in the are known to those of skill in the art, and hence, in view of the teachings in the specification, one of skill in the art, routinely can select bacterial species to practice the methods. It is emphasized that the bacteria for use in the claimed methods are not any bacteria, as alleged in the Office Action, but rather, bacteria that are detectable, replication competent, non-pathogenic or attenuated and recognized by the immune system. Selection of bacteria with these properties is known in the art and taught in the application. Furthermore, use of such bacteria in the methods as claimed to detect wounded and inflamed tissues is reproducible and based on known methods and reagents, and

this is predictable. The level of skill in the art is high, and knowledge of those of skill in the art is extensive, and there is a body of prior art that describes preparation of the reagents and use of the detection methods required for practice of the claimed methods. Thus, it would not require undue experimentation to practice the methods as claimed.

Applicant is entitled to claims that are commensurate in scope not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed. In the instant application, Applicant discloses to the public methods for the detection of wounded or inflamed tissue using known bacterial species that are detectable and known for detection by known methods. Among Applicant's contributions, is the new use for the non-targeted bacteria for detection wounded/inflamed tissues or sites. The specification clearly shows that bacteria with the properties recited in the claims accumulate at such sites and can be detected at such sites.

Therefore, in view of the breadth of the claims, the high level of skill of those in the art, the knowledge of those of skill in the art, the teachings in the prior art, the teachings in the application, the working examples in the application, and the demonstrated repeatability of the method as claimed, it would not require undue experimentation to practice the methods as claimed. Thus, the claims are not broader than the enabling disclosure.

REBUTTAL TO THE EXAMINER'S ARGUMENTS

a. Rebuttal to Examiner's argument that colonization is bacterial-strain dependent and administration dependent

On page 16 of the Office Action, the Examiner alleges:

> In support of the claimed invention, Applicant discloses that luminescent S. typhimurium and V. cholera injected into the femoral vein of nude mice and C57BU57 specifically accumulated at the site of cutaneous wounds. (Example 2, Figures 2-4.) It is noted, however, that the data presented (which consists of a single mouse for each condition) appear to show that the accumulation of bacteria depends on the strain of bacteria used, the location of the wound and the strain of mouse. For example, the nude mouse injected with Salmonella exhibits accumulation of bacteria at the leg wound and ear tag (Figure 2B), the nude mouse injected with Vibrio exhibits accumulation only at the leg wound (Figure 3B), while the immunocompetent mouse exhibits accumulation of Vibrio only at the ear tag (Figure 4). Thus, the working examples demonstrate that the accumulation of any given strain of bacteria at any given wound in any given animal is highly variable and unpredictable.

As discussed above, and shown in the application, bacteria for use in the methods are known, and the methods for detection of the bacteria are known. As discussed above, the bacteria and means for detection/visualization are known reagents that can be used in the

instantly claimed methods. The application teaches that bacteria accumulate in wounds/inflamed tissues/sites and demonstrates that with working examples using three different strains. There is no basis for the Examiner to conclude that other strains known to have the properties recited in the claims do not accumulate in wounds/inflamed tissues/sites. Further, if needed, one of skill in the art can test a candidate strain that meets the recited criteria exactly as taught in the specification to confirm that the strain accumulates. No knowledge of the mechanism for accumulation is needed. Further as described above, detection/visualization methods are known to those of skill in the art and also are described in the application. One of skill in the art can employ any such method.

The Examiner has cited statements set forth in of the specification to support the argument that the distribution pattern of any particular bacteria is not reasonably predictable. The distribution pattern of any particular bacteria readily can be tested as shown in the application. The cited sections and accompanying working examples, however, show that regardless of any differences in distribution profiles or kinetics, **the tested microorganisms consistently localized at sites of inflammation or wounds** within a subject. **Thus, accumulation is not dependent on the initial distribution.** As claimed, the subject is monitored to determine where bacteria accumulate, not to assess an initial distribution pattern.

The particular sections of the specification that cite differences between the distribution of attenuated *Salmonella typhimurium* and attenuated *Vibrio cholerae* described in Example 2 refer only to the initial observation period only (0-60 minutes) for the experiment; the method demonstrated in the experiment is the monitoring of accumulation. As described in the specification, the experiment involves the injection of attenuated *Salmonella typhimurium* and attenuated *Vibrio cholerae* (each carrying the pLITE201 plasmid for expression of bacterial luciferase) into the left femoral vein of anesthetized mice. Prior to the injection, the left femoral vein was exposed by making a 1 cm incision with a surgical blade. Following injection of the bacteria, the incision was closed with 6-0 sutures, and the mice were then monitored under a low light imager for photon emission. The results for the initial distribution of the bacterial strains following injection into the mice were shown in Figure 1 of the application and described in Example 2. As stated in Example 2 of the specification:

> Injection of attenuated S. typhimurium caused wide dissemination of the bacteria throughout the body of the animals (FIG. 1A). This pattern of distribution was visible

> within 5 minutes after bacterial injection and continued to be detected at the one-hour observation period. Injection of attenuated V. cholera into the bloodstream, however, resulted in light emission that was localized to the liver within 5 minutes after bacterial injection and remained visible in the liver at the one-hour observation period (FIG. 1B).

During the initial observation period only, *V. cholera* was seen to localize to the liver and S. *typhimurium* was more widely distributed throughout the animal. One of the primary functions of the liver, widely known at the time of filing of the application, is to clear toxins and foreign materials from the bloodstream. Thus, injected bacteria will accumulate in the liver soon after injection. In view of the knowledge about the liver at the time of the priority date of the application, and the teachings in the specification, one of skill in the art **would not interpret** this initial localization to the liver at five minutes post-injection of the bacteria to indicate that the liver is a site of a wounded or inflamed tissue. The method as described requires monitoring to assess accumulation. Regardless of any reasons why the bacterial strains may have differed in their accumulation in the liver during the initial observation period, this difference had no impact on the results of the experiment, in which both strains exhibited accumulation in the wounded and inflamed tissues after clearance of the initial wave of distribution as shown in Figure 2.

It respectfully is submitted that the statement in Example 2 that "the distribution pattern of light emission following an intravenous injection of bacteria into the mice was bacterial-strain-dependent" should not be taken out of context of the experiment as a whole. The statement refers only to the initial observation period of the experiment and has no bearing on the outcome, namely, both bacterial strains accumulated in the wounded/inflamed tissues and not in uninjured tissues. This clearly is shown in Figure 2 as well as stated in specification:

> Imaging the same animals 48 h after bacterial injection showed that **all** of the detectable light emission from the earlier time had diminished and was eliminated completely from the injected animal with the exception of the inflamed wounded tissues such as the incision wound and the ear tag region...Careful examination of individually excised organs as well as blood samples from infected animals confirmed the absence of luminescence in these normal uninjured tissues."[emphasis added].

Hence, the Examiner's assertion regarding the difference in the distribution among the bacterial strains has no bearing on the ability of both tested strains to accumulate in wound/inflamed tissues, as supported by the Examples. Furthermore, with reference the the data shown in the Figures, it is emphasized that the leg wound in Figure 4 would not be visible from the dorsal view shown, which allows observation of the ear tag wound. Also, it

is noted that bacteria do not accumulate at sites that are not inflamed or have healed. Hence, the bacteria will not accumulate at an ear tag that is healed or not inflamed. The application shows that bacteria accumulate in wounded/inflamed tissues/sites and are cleared from healthy tissues. Thus, differences in initial distribution of bacteria has no bearing on practice of the claimed methods.

b. Rebuttal to Examiner's argument that Yu *et al.* (2003) demonstrates that the Art is not enabling of the breadth of Applicant's claims

While further rebuttal to the Examiner's comments are set forth below, it is pertinent to discuss the Yu *et al.*, cited by the Examiner on pages 8 and 9 of the Office Action. Examiner maintains that Yu *et al.* (2003) demonstrates Yu *et al.* demonstrates that bacteria, viruses or mammalian cells, when administered to subjects, accumulate in cancerous tissues, but not in any tissue recited in the claimed subject matter. The Examiner further alleges that Yu *et al.* teaches that the mechanism of bacterial colonization is unknown, that administration type-dependent colonization is common and that it is not "predictable" which administration will yield which colonization type.

First, Yu *et al.*, employs tumor models, **not** inflammation/wound models, and shows that bacteria accumulate in tumorous tissue. Yu *et al.* does not show anything regarding wounded or inflamed tissues/sites. Yu *et al.*, which published after the earliest priority date of the instant application date, describes methods for detection of tumors. Hence, it is not pertinent to the methods of the instant claims. Therefore, the Examiner's statement that Yu *et al.* is not enabling for the instantly claimed subject matter, is inapt, since Yu *et al.* is directed to different subject matter and is published subsequent to the priority date of the instant application. Yu *et al.*, is irrelevant to whether or not the application teaches how to make and/or use the claimed method, which is for detecting wounds/inflamed tissues.

Second, knowledge of the mechanism of colonization or colonization-type is irrelevant to the practice of the methods as claimed. By following the teachings of the specification, the bacteria are administered, and, as taught and demonstrated in the application, bacteria, with the recited properties, accumulate at wounded/inflamed tissues/sites. The teachings of the specification, in light of the state of the art and the knowledge of those of skill in the art, allow one of skill in the art to practice the steps of the methods as claimed. Knowledge of the mechanism of localization or the types of colonies visualized at the sites of localization, is not needed. The specification teaches and

demonstrates that bacteria that are recognized by the immune system and that are nonpathogenic or attenuated accumulate at such sites/tissues.

As discussed above, to demonstrate the full scope of enablement of the claimed methods, Applicant is not required to demonstrate a completely optimized procedure as long as it is possible to successfully perform the method as claimed without undue experimentation. Contrary to the assertion of the Office Action, the ability to practice the methods as claimed is not dependent on the particular bacterium that is used in the method. Instead the non-pathogenic or attenuated microorganism or cell is a tool that is used to detect abnormal conditions in a subject, such a wound or inflamed tissue, a foreign object (*e.g.*, a suture), or a disease or condition associated with wounded or inflamed tissue. It is not a characteristic of the particular microorganism or cell per se that provides for specific colonization of the wounded or inflamed tissue, but rather is the protective environment of the wounded or inflamed tissue (from the immune system) that leads to accumulation of bacteria in such sites. The bacteria administered are cleared by the immune system from non-wounded or non-inflamed tissues. Hence, any non-pathogenic or attenuated microorganism or cell that is recognized by the immune system should accumulate in wounded or inflamed tissue as taught by the specification. The claimed methods are thus applicable to any non-pathogenic or attenuated microorganism or cell that is recognized by the immune system. Such microorganisms and cells will be cleared from most tissues/sites, but not from wounded/inflamed tissues/sites.

c. Rebuttal Examiner's argument that the claims are not enabled for detecting an atherosclerotic plaque

On page 9 of the office action, the Examiner asserts that:

> With regard to accumulation of any microorganism at sites of inflammation other than wounds or tissue into which a foreign object has been introduced, e.g., an atherosclerotic lesion, the application refers to reports providing evidence that C. Pneumonia, I3 pylori, CMV and HSV have been found in atherosclerotic plaques and speculates that intravenously administered microorganisms and cells will penetrate into atherosclerotic plaques where they will replicate to a sufficient degree that they will be capable of indicating the presence of a plaque. (See especially the paragraph bridging pages 13-14.) However, no evidence is presented to indicate that any intravenously administered microorganism or cell would be capable of selective accumulation within an atherosclerotic lesion such that it could actually be used to identify the location of the lesion as claimed.

It respectfully is submitted that the application demonstrates that bacteria as claimed accumulate in wounded tissues and inflamed tissues within a subject. Those of skill in the art know that atherosclerotic plaques are inflamed lesions and their locus is known.

Atherosclerosis is a chronic inflammatory response in the arteries. Bacteria, with the requisite properties (recognized by the immune system and replicate in the subject) will, upon administration, will be recognized by the immune system and cleared from non-wounded, non-inflamed tissues, but will, by virtue of the immunoprivileged nature of wounded and inflamed tissues, will not be cleared from such tissues and will accumulate and will be detected. Thus, detection of accumulated bacteria in the arteries is indicative of an atherosclerotic plaque.

Policy Considerations

As demonstrated by the above of the *In re Wands* factors, the teachings of the specification, when combined with the knowledge of those of skill in the art and the ability to repeatedly and successfully (i.e., predictably) execute the various steps, leads to the conclusion that each of the steps of the instant methods could be performed without undue experimentation. As discussed above, administration of microorganisms for the detection of wounded or inflamed tissue was successfully demonstrated using a variety of microorganisms by following the teachings of the instant application and by an extensive body of knowledge in the art as of the application's earliest priority date.

Applicant is entitled to claims that are commensurate in scope, not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed. In the instant application, Applicant provides the public with methods for the detection of a wound, wounded tissue, an inflammation site, inflamed tissue thereof by administering and detecting a variety of microorganisms or cells that accumulate at such sites. As a broad body of knowledge is available in the areas of microbiology, genetic manipulation of microorganisms and cells, administration of microorganisms and cells to subjects, and *in vivo* detection techniques for detecting the administered microorganisms and cells, and the application teaches bacteria for use in the method and how to identify such bacteria, and provides working examples with three diverse species, it would be unfair and contrary to the Constitutional mandate set forth in Article, Section 8, to require applicant to limit the claims to any particular embodiment or to deny patent protection at all. To do so would permit those of skill in the art to practice the methods as described in the application with any bacterium that has the requisite properties using known detection/visualization method and avoid infringing such limited claims.

See, e.g., In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970).

The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

III. PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION OVER U.S. PATENT APPLICATION NO. 10/516,785

Claims 1, 2, 6, 7, 9, 12, 14, 16, 18 and 20-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over Claims 33-35, 39, 45, 46, 51, 52, 54, 55, 64, 65, 67-72, 74, 75, 77 and 78 of U.S. Application Serial No. 10/516,785. It is respectfully submitted that U.S. Application Serial No. 10/516,785 was abandoned, thereby rendering this rejection moot.

IV. REJECTION OF CLAIMS 1, 2, 6, 12, 14, 18 and 20-22 UNDER 35 U.S.C. §102

A. Rejection of Claims 1, 2, 6, 12, 14, 18 and 20-22 under 35 U.S.C. §102(b)

Claims 1, 2, 6, 12, 14, 18 and 20-22 are rejected under 35 U.S.C. 102(b) as anticipated by Costa *et al.* (2001) *J. Immunol.* 167:2379-2387 as evidenced by post-filing date Wade *et al.* (2006) *Am. J. Respir. Cell Mol. Biol.* 34:727-737 and Weissledcr *ct al.* (2001) *Radiol.* 219:316-333 because Costa *et al.* discloses a method in which myelin basic protein (MBP)-specific $CD4^+$ T cells are infused into mice that are immunized with MBP to mice and the mice are monitored for accumulation in CNS cells that express the autoantigen. This rejection respectfully is traversed.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of skill in the art in

possession of the invention. An inherent property has to flow naturally from what is taught in a reference. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the 'prior art' . . . the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). *In re Arkey, Eardly, and Long*, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

The Claims

Claim 1 is discussed above.

Costa *et al.*

Costa *et al.* discloses intraperitoneal injection of MBP-specific $CD4^+$ T cells that express yellow fluorescent protein (YFP) into a mouse model of autoimmune encephalomyelitis in which the mice were MBP-immunized. The reference discloses that following injection, the MBP-$CD4^+$ T cells traffic to the sites of autoimmune lesions in the central nervous system. The autoimmune lesions are detected by detecting the fluorescence signal output from the cells using bioluminescent imaging with a cooled charge-coupled device (CCD) camera. The location of the lesion was detected by detecting the location of the $CD4^+$ T cells.

Costa *et al.* does not disclose any method, which involves administration of bacteria to a subject, nor does it disclose a method of detecting a wound or inflammation by detecting accumulation of a bacterium at a wounded or inflamed tissue. Therefore, since anticipation requires disclosure of all elements as claimed, Costa *et al.* does not anticipate claim 1, nor any claim dependent thereon.

B. Rejection of Claims 1, 7, 9 and 20 under 35 U.S.C. §102(b)

Claims 1, 7, 9 and 20 are rejected under 35 U.S.C. 102(b) as anticipated by Hamblin *et al.* (2002) *Photochem. Photobiol.* 75:51-57. This rejection respectfully is traversed.

Relevant Law

See above.

The Claims

The claims are discussed above.

Hamblin *et al.*

Hamblin *et al.* discloses administration of a bioluminescent strain of *E. coli* directly into a visible incision wound on a mouse. For administration of the bacteria, the reference describes in column 2 on page 52 that:

> Four full-thickness excisional wounds were made in a line along the dorsal surface...using surgical scissors and forceps...A suspension (50 pL PBS) containing $5x10^6$ cells of midlog phase E. coli (10^8 cells mL^{-2}) was inoculated ***into each wound***, and the mouse was imaged with luminescence to ensure equal bacterial loading into each wound. [emphasis added].

The bacteria administered to the mice express the *lux* operon from *Photohaddus luminscens* and are monitored at the wound by detection of luminescence. Hamblin *et al.* thus discloses monitoring of bacteria in a wound that has already been detected on a mouse. Hamblin *et al.* does not disclose detection of a wounded or inflamed tissue within a subject.

Disclosure of Hamblin *et al.* and differences from the instant claims

The instant claims are directed to a method of detecting a wounded or inflamed tissue *within* a subject by administering bacteria to a subject for whom the presence or absence of wound is to be detected. Hamblin et al. does not disclose detection of a wound since the wound is visible. Hamblin et al. does not disclose detection of a wound within a subject in whom a wound is to be detected. The wound is visibly detected prior to administration of the bacteria. Hamblin *et al.* detects expression of the lux operon in order to control loading of the bacteria into each wound. Hence detection is for quantitating bacteria, not detecting wounds. Hamblin *al.* does not disclose *detection* of a wound *within a subject* because the bacteria are administered directly to the wound. Hence, Hamblin *et al.* does not disclose *detection* of a wounded or inflamed tissue within a subject.

Therefore, Hamblin *et al.* fails to disclose several elements as claimed, including detection of a wound within a subject. Because Hamblin *et al.* does not all elements as claimed, the reference does not anticipate claim 1, nor any dependent claim thereon.

V. THE REJECTION OF CLAIM 16 UNDER 35 U.S.C. §103(a)

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Costa *et al.* (2001) *J. Immunol.* 167:2379-2387 in view of Weissledcr *ct al.* (2001) *Radiol.* 219:316-333

because, while Costa *et al.* fails to teach a method where monitoring is performed by MRI, "Weissleder *et al.* teaches that MRI imaging using proteins such as transferrin was known in the art as an alternative to optical imaging as used in the method of Costa et al." (page 18). This rejection respectfully is traversed.

Relevant Law

To establish prima facie obviousness under 35 U.S.C. §103, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). This principle of U.S. law regarding obviousness was not altered by the recent Supreme Court holding in KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ2d 1385 (2007). In KSR, the Supreme Court stated that "Section 103 forbids issuance of a patent when 'the differences between the subject m*att*er sought to be patented and the prior art are such the subject m*att*er as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject m*att*er pertains.'" KSR Int'l Co. v. Teleflex Inc., 127 S.Ct. 1727, 1734, 82 USPQ2d 1385, 1391 (2007).

The question of obviousness is resolved on the basis of underlying factual determinations including (1) the scope and content of the prior art, (2) any differences between the claimed subject m*att*er and the prior art, (3) the level of skill in the art. Graham v. John Deere Co., 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). See also KSR, 127 S.Ct. at 1734, 82 USPQ2d at 1391 ("While the sequence of these questions might be reordered in any particular case, the [Graham] factors continue to define the inquiry that controls.") The Court in Graham noted that evidence of secondary considerations, such as commercial success, long felt but unsolved needs, failure of others, etc., "might be utilized to give light to the circumstances surrounding the origin of the subject m*att*er sought to be patented." 383 U.S. at 18, 148 USPQ at 467. Furthermore, the Court in KSR took the opportunity to reiterate a second long-standing principle of U.S. law: that a holding of obviousness requires the fact finder (here, the Examiner), to make explicit the analysis supporting a rejection under 35 U.S.C. 103, stating that "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. Id. at 1740-41, 82 USPQ2d at 1396 (citing In re Kahn, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance

of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. KSR, 127 S. Ct. at 1731. The court stated in dicta that, where there is a "market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try **might** show that it was obvious under § 103."

In a post-KSR decision, PharmaStem Therapeutics. Inc. v. ViaCell. Inc., 491 F.3d 1342 (Fed. Cir. 2007), the Federal Circuit stated that:

> an invention would not be invalid for obviousness if the inventor would have been motivated to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. Likewise, an invention would not be deemed obvious if all that was suggested was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

Furthermore, KSR has not overruled See In re Papesch, (315 F.2d 381, 137 USPQ 43 (CCPA 1963)), In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991), and In re Deuel (51 F.3d 1552, 1558-59, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995)). "In cases involving new compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007).

The mere fact that prior art may be modified to produce the claimed subjected does not make the modification obvious unless the prior art suggests the desirability of the modification. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); see, also, *In re Papesh*, 315 F.2d 381, 137 U.S.P.Q. 43 (CCPA 1963). In addition, if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

As always, unexpected properties must always be considered in the determination of obviousness. A compound's structure and properties are inseparable so that unexpected properties are part of the subject matter as a whole. *In re Papesch*, 315 F.2d 381, 391, 137 USPQ 43, 51 (CCPA 1963)

The disclosure of the applicant cannot be used to hunt through the prior art for the claimed elements and then combine them as claimed. In re Laskowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989). "To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher" W.L. Gore & Associates, Inc. v. Garlock Inc., 721 F.2d 1540, 1553, 220 USPQ 303, 312-13 (Fed. Cir. 1983).

The rejected claim

Claim 16 is directed to a method of detecting a wound, wounded tissue or inflamed tissue or a disease associated therewith in a subject by administering a bacterium and monitoring the subject to detect the accumulation of the bacterium at the wound, wounded tissue or inflamed tissue, where the monitoring is performed by magnetic resonance imaging (MRI).

Teachings of the cited references and differences from the claimed method

Costa *et al.*

Costa *et al.* teaches intraperitoneal injection of MBP-specific $CD4^+$ T cells for detection autoimmune lesions that express MBP in the central nervous system. Costa *et al.* does not teach or suggest any method that involves administration of bacteria to a subject for detection of wounded or inflamed tissue.

Weissledcr *ct al.*

Weissleder *et al.* does not cure the deficiencies in the teachings of Costa *et al.* Weissleder *et al.* teaches MRI imaging using proteins such as transferrin. Weissleder *et al.* does not teach or suggest a method detecting a wounded or inflamed tissue within a subject by administration of bacteria.

Analysis

The combination of teachings of Costa *et al.* and Weissleder *et al.* do not result in the instantly claimed methods

The instant claims are directed to a method of detecting a wounded or inflamed tissue *within* a subject by administering bacteria to a subject for whom the presence or absence of wound is to be detected. Costa *et al.* teaches detection of autoimmune lesion by administering targeted mammalian cells to a subject. There is no teaching or suggestion of for detecting any wounded or inflamed tissue within a subject via administration of a

bacterium. Costa *et al.* does not teach or suggest that bacteria or any cells accumulate in wounded or inflamed cells. Weissleder *et al.* does not cure these deficiencies.

Furthermore, there is not teaching or suggestion in either reference to do that which applicant has done (In re Fritch). No art of record teaches or suggests that bacteria having the recited properties accumulate in wounds or inflamed tissues within a subject. Thus, there is no teaching or suggestion to do that which applicant has done.

Therefore, the combination of teachings of the references does not result in the instantly claimed methods. The Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above, reconsideration and allowance of the application respectfully are requested.

Respectfully submitted,

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